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Title : New indoline compounds
Art Unit : 1625
Examiner : Evelyn HUANG

Honorable Commissioner of Patents and Trademarks
Alexandria, VA 22313

DECLARATION UNDER 37 CFR 1.132

I, Mark J. MILLAN, a citizen of the United Kingdom, of 19, rue du Président Wilson, 78230 LE PECQ, France, declare and say that:

I hold the degrees of Bachelor of Arts (1978), Master of Arts (1983), and Doctor of Sciences (1985) from the University of Cambridge (England).

Since 1995, I have been Director of the Division of Psychopharmacology at the Institut de Recherches Servier, France.

I am the author or co-author of more than 550 international publications such as patents, scientific publications and communications.

I am one of the co-inventors of US Patent Application Serial n° 10/813,347
filed June 7, 2004 concerning "New diphenylurea compounds".

I am thoroughly familiar with the above-mentioned patent application and fully support the pharmacological data contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived and the arguments presented as concerns the therapeutic interest of the compounds described.

The compounds of the present invention have pharmacological properties that allow their use in the treatment of disorders of the central nervous system.

Throughout this Declaration, we present a large body of literature that underpins the correlation between the pharmacological activity of the compounds and their potential utility in the treatment of psychiatric and other CNS disorders.

The compounds disclosed in the present application displayed marked *in vivo* activity in pharmacological tests as demonstrated in Examples 5 to 8 of the present Patent Application as filed.

As acknowledged by the Office, 5-HT_{2C} receptors play an important role in the control of depressive states as well as bulimia and anorexia and the following information underpins their employment in the management of schizophrenia, sleep disorders, sexual dysfunction and libido disorders, impulsive disorders, migraine, cognitive disorders and Parkinson's disease.

EXAMPLE 6 : Penile erection test following administration of Ro 60-0175 (1.25 mg/kg, s.c.) in the rat

Use of a well-established and highly-specific pharmacological model demonstrated that the compounds behave as 5-HT_{2C} receptor antagonists *in vivo* in blocking the induction of penile erections by the selective 5-HT_{2C} receptor agonist, Ro 60-0175.

1- "Involvement of 5-HT_{2C} receptors in drug-induced penile erections in rats", H.G., Berendsen et al, *Psychopharmacology*, 101, 57-61 (1990);

2- "5-HT_{2C} receptors mediate penile erections in rat: actions of novel and selective agonists and antagonists" M.J. Millan, et al, *European Journal of Pharmacology*, 325, 9-12 (1997).

Recent articles have provided evidence for beneficial effects of 5-HT_{2C} receptor antagonist properties in the treatment of schizophrenia:

3- "5-HT_2 receptor antagonism reduces hyperactivity induced by amphetamine cocaine, and MK-801 but not D_1 agonist C-APB", M.F. O'Neill et al., *Pharmacology Biochemistry and Behavior*, 63, 2, 237-243 (1999);

4- "Attenuation of haloperidol-induced catalepsy by 5-HT_{2C} receptor antagonist", C. Reavill et al., *British Journal of Psychopharmacology*, 126, 572-574 (1999);

5- "Inverse antagonist activity of atypical antipsychotic drugs at human 5-hydroxytryptamine2C receptors", K. Herrick-Davis et al., *Journal of Pharmacology and Experimental Therapeutics*, 295, 1, 226-232 (2000);

6- "5-HT_{2C} receptor antagonist: potential in schizophrenia" M.D. Wood et al, *Drug Development Research* 54, 88-94 (2001).

Substantial evidence supports the argument that 5-HT_{2C} receptor antagonists may be of use in the treatment of sleep disorders:

7- "Effects of ritanserin on sleep disturbances of dysthymic patients", T. Paiva et al., *Psychopharmacology*, 96, 395-399 (1988);

8- "Functional activity of 5-HT_2 receptors in the modulation of the sleep/wakefulness states". C. Dugovic *Journal Sleep Research* 1 1163-168 (1992);

9- "Serotonin-2 receptors and human sleep: effect of a selective antagonist on EEG, power spectra", H.P. Landolt et al., *Neuropsychopharmacology*, 21, 455-466 (1999);

10- "Olanzapine increases slow-wave sleep: evidence for blockade of central of 5-HT_{2C} receptors in vivo", A.L. Sharpley et al., *Biological Psychiatry*, 47, 468-470 (2000).

Moreover, as cited by the Examiner, in "A review of central 5-HT receptors and their function", *Neuropharmacology,* 38, 1083-1152 (1999), Barnes and Sharp declare that 5-HT_{2C} receptors may be of importance to sleep disorders (page 1110, left column, lines1-2). This was also clearly mentioned in another paper citer by the Examiner "Serotonin agonist and antagonists", I. Wijngaarden, et al, *Recueil des Travaux Chimiques de Pays-Bas,* 112, (1993), page 128, right column, lines 26-29: *"ritanserin improves the quality of sleep"*.

There is also evidence for a beneficial influence of 5-HT_{2C} receptor antagonists in the treatment of sexual dysfunction and libido disorders:

11-"DOI-induced inhibition of copulatory behavior in male rats: reversal by 5-HT_2 antagonists", N.V. Watson, B.B. Gorzalka, *Pharmacological Biochemistry and Behavior*, 39, 605-612 (1991);

12- "The role of the 5-HT_2 receptor in the regulation of sexual performance of male rats", M.M. Foreman et al., *Life Sciences*, 45, 1263-1270 (1989);

13- "Clozapine acts as a 5-HT_2 antagonist by attenuating DOI-induced inhibition of male rat sexual behavior", T. Klint, K. Larsson, *Psychopharmacology*, 119, 291-294 (1995);

14- "Care of the sexually active depressed patient. R.M. Hirschfeld. *Journal of Clinical Psychiatry.* 60 Suppl 17:32-35 (1999);

15- "5-HT_{2A} and 5-HT_{2C} receptors differentially modulate sexual arousal in the presence of a female", N.K. Popova, T.G. Amstislavaskaya, *Neuroendocrinology* 76, 28-34 (2002);

16- "Amesergide, LY-237733", *Pharmaproject*, Phase II clinical trial (2005).

There are data suggesting that drugs possessing antagonist actions at 5-HT_{2C} receptors can attenuate impulsive behavior.

17- "5-HT_2 receptor activation enhances impulsive responding without increasing motor activity in rats" T. Koskinin et al., *Pharmacology, Biochemistry and Behavior*, 66, 729-738 (2000);

18- "Effects of serotonergic agents on isolation-induced aggression" S.M. White et al,. *Pharmacology Biochemistry and Behavior*, 39, 729-36 (1991).

Moreover, clomipramine, an antidepressant drug possessing potent 5-HT_{2C} receptor antagonist properties, is used to treat impulsive states in man.

19- "S 33005 a novel ligand at both serotonin and norephedrine transporters: II. Behavioral profile in comparison with venlafaxine, reboxetine, citalopram and clomipramine", M.J. Millan et al., *Journal of. Pharmacology and Experimental Therapeutics.*, 298, 581-591 (2001);.

20- "Multicentre, double-blind, comparison of fluvoxamine and clomipramine in the treatment of obsessive-compulsive disorder", E. Mundo et al., *International Clinical Psychopharmacology.* 15, 69-76 (2000).

There is evidence that antagonist properties at 5-HT2C receptors may be of importance in the prevention of migraine.

21- "The induction of pain: an integrative review", M.J. Millan, *Prog. Neurobiol.*, 57, 1-164 (1999);

22- "Descending control of pain", M.J. Millan, *Prog. Neurobiol.*, 66, 355-474 (2002);

23- "Hypersensitivity to meta-chlorophenylpiperazine (mCPP) in migraine and drug withdrawal", H.O. Kalkman, *Int. J. Clin. Pharmacol. Res.*, 17, 75-77 (1997);

24- "5-Hydroxytryptamine (5-HT) and the initiation of migraine: new perspectives", J.R Fozard., H.O. Kalkman, *Naunyn. Schmiedebergs Arch. Pharmacol.*, 350, 225-229 (1994);

25- "Is migraine prophylactic activity caused by 5-HT_{2B} or 5-HT_{2C} receptor blockade?", H.O. Kalkman, *Life Sci.*, 54, 641-644 (1994).

In addition, the following drugs, which possess antagonist properties at 5-HT_{2C} receptors are, or have been, under development for this indication:

26- "Ro-60-0759", *Pharmaproject*, Preclinical trial (2005);

27- "SB-243213", *Pharmaproject*, Phase I clinical trial (2005);

28- "LY-053857", *Pharmaproject*, Phase II clinical trial (2005).

Moreover, 5-HT_{2C} receptor antagonists are of potential use in the management of cognitive disorders. Thus, activation of 5-HT_{2C} receptors compromises learning and memory, suggesting that their blockade should be associated with pro-cognitive properties.

29- "Effects of the serotonin agonists 8-OH-DPAT, buspirone, and DOI on water maze performance", G.J. Kant, R.M. Wylie, K. Chu, S. Ghosh, *Pharmacol. Biochem. Behav.*, 59, 729-735 (1998);

30- "Role of 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} receptors in learning", A. Meneses , E. Hong, *Behav. Brain Res.*, 87, 105-110 (1997).

31- "Effects of the serotonin receptor agonists 8-OH-DPAT and TFMPP on learning as assessed using a novel water maze", G.J. Kant, G.R. Meininger, K.R. Maughan, W.L. Wright, T.N. Robinson, 3rd, Neely TM, *Pharmacol. Biochem. Behav.*, 53, 385-390 (1996).

Further, frontocortical adrenergic projections, together with frontocortical and striatal dopaminergic pathways, play an important role in favouring cognitive-attentional function and their activity is enhanced by blockade of 5-HT_{2C} receptors.

EXAMPLE 5: Measurement of the extracellular concentrations of dopamine and noradrenaline in the frontal cortex of the conscious rat

32- "Serotonin/dopamine interaction-focus on 5-HT_{2C} receptor, a new target of psychotropic drugs", G. Di Giovanni, V. Di Matteo, E. Esposito, *Indian J. Exp. Biol.*, 40, 1344-1352 (2002);

33- "The nigrostriatal dopamine system: a neglected target for 5-HT_{2C} receptors", P. De Deurwaerdere, U. Spampinato, *Trends Pharmacol. Sci.*, 22, 502-504 (2001);

34- "Serotonin (5-HT)$_{2C}$ receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo", M.J. Millan, A. Dekeyne, A. Gobert, *Neuropharmacology*, 37, 953-955 (1998).

Indeed, as commented by Barnes and Sharp in a publication cited by the Examiner ["A review of central 5-HT receptors and their function", *Neuropharmacology,* 38, (1999), page 1109, right column, lines 46-53], Millan M.J. et al. reported "*that 5-HT$_{2C}$ receptor blockade increases the release of noradrenaline and dopamine in microdialysis experiments*" which suggests "*that 5-HT$_{2C}$ receptors exert a tonic inhibitory influence on mesocortical/mesolombic dopaminergic and noradrenergic projections*" [ref. 34 above].

Finally, 5-HT$_{2C}$ receptor antagonists are of potential use in the management of Parkinson's disease.

35- "A role for 5-HT$_{2C}$ antagonists in the treatment of Parkinson's disease", S.H. Fox, J.M. Brotchie, *Drug News and Perspectives,* 12, 477-483 (1999);

36- "5-HT$_{2C}$ receptor binding is increased in the substantia nigra pars reticulata in Parkinson's disease", S.H. Fox, J.M. Brotchie, *Movement Disorders,* 15:1064-1069 (2000).

Conclusion

In conclusion, compounds of US Serial 10/813,347 exert antagonist properties at 5-HT$_{2C}$ receptors *in vivo* (see Examples 5-8 of the Present Application). In light of extensive literature support (publications enclosed), and the clear correlation between 5-HT$_{2C}$ antagonist properties of the compounds and the diseases to be treated ("background of the invention"), we contend that compounds of US Serial n° 10/813,347 are of potential utility in the treatment of depression, bulimia, and anorexia (as accepted by the Office), as well as schizophrenia, sleep disorders, migraine, impulsive disorders, libido disorders, cognitive disorders and Parkinson's disease.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

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Executed at: Croissy 03.03.05

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